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THE SIGNIFICANCE OF THE CHANGES IN THE SO-CALLED PAN-  
DEMIC INFLUENZA.

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In spite of the fact that the recently prevailing pandemic infection popularly known as influenza has been made the subject of innumerable investigations, its cause still is a matter of doubt. Until the identity of the provocative agent is established, speculation as to the sequence of events is more profitably to be based on anatomical and clinical correlations than on the insecure results of bacteriological endeavor as thus far unfolded. In the so-called pandemic influenza, the initial effect of the provocative agent, whatever its nature and origin may be—filterable virus or what not—appears to be exerted on the vascular system, so altering the circulation as to produce an extraordinary degree of capillary dilatation and congestion in the skin, mucous membranes and viscera, simultaneously apparently, or approximately so. A knowledge of the pathology of the circulatory changes is valuable both from the viewpoint of treatment and the interpretation of symptoms.

The extraordinary vascular dilatation and the concomitant tendency to hemorrhage are comparable to the effects of certain poisons. For example, in a case of trinitrotoluene poisoning, I observed bilaterally distributed hemorrhagic foci in the lungs that gave to these organs naked eye appearances strikingly like those of the so-called influenza, and similar hemorrhagic foci are not uncommonly to be found in the lungs as a result of death from mor-

phine, cocaine and other alkaloids. A counterfeit is also to be seen in acute poisoning by methyl alcohol. In the course of the past year, a large number of such cases were investigated by Dr. Charles Norris, chief medical examiner of the city of New York, and his first assistant, Dr. Benjamin Schwartz. The chemical and microscopical examinations were carried out in the Bellevue Hospital laboratories. In acute methyl alcohol poisoning hemorrhagic foci in the lungs are not uncommon and in at least some of the cases the naked eye resemblance to the pneumonic lesions of the so-called influenza is impressive. The comparison, moreover, is borne out by the remarkable degree of capillary dilatation to be found in the meninges of the brain and in the liver, kidneys and suprarenal capsules in both conditions. In morphine poisoning and in tetanus the vascular injection of the cerebral meninges is likewise comparable to that of the so-called influenza.

It is recognized that, early in the course of the so-called pandemic influenza, the conjunctivæ and the skin of the face, neck and upper chest are suffused, and that later this duskiess may be replaced by cyanosis, added to which such symptoms as dermatographia and the white line of Sergeant still further indicate the instability of vascular control. One of the most illuminating signs of circulatory embarrassment, however,—a change which sometimes is to be observed before there are any detectable evidences of pneumonic involvement—is that the blood pressure is low, on occasions alarmingly so, and that the pulse is often slow, even in patients who have not received digitalis. In connection with the phenomenon of low blood pressure and as tending to prove the occurrence of visceral congestion previous to the onset of pneumonia, it is significant that, in the recently prevailing disease, postmortem examination revealed

congestion of the medullæ of the suprarenal capsules in no small proportion of cases. Microscopically, the medullary capillaries in these circumstances are distended to a degree rarely encountered in infective diseases, with the exception of diphtheria<sup>1</sup> and bubonic plague and in certain forms of sepsis, especially in children, and even hemorrhages into the substance of the gland may be observed. In one of the Bellevue Hospital autopsies, thrombosis of the suprarenal veins was present and identical lesions have been described by others. In some respects the action of the provocative agent on the circulation is not unlike that of certain members of the nitrite series, particularly with regard to the flushed skin, low blood pressure and dilatation of the capillaries in the splanchnic area. On the other hand, it is scarcely conceivable that conditions such as have been described in the adrenal medullæ are compatible with proper function, but that embarrassment of the adrenal circulation must interfere with the manufacture and discharge of those products of the gland which have to do with the regulation of blood pressure, thus furnishing at least a contributing factor in the lowering of vascular tension. The conception of suprarenal insufficiency is furthermore substantiated by the profound asthenia which so commonly is observed in this peculiar infection.

Finally, it is a matter of observation that the pneumonia associated with the so-called influenza is practically always preceded by intense injection of the capillaries in the mucous membrane of the

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<sup>1</sup>The presence of marked congestion and even hemorrhages in the suprarenal medullæ of children dead of diphtheria is a well known fact among pathologists. Identical lesions occur in guineapigs that have been injected for the determination of the virulence of different strains of diphtheria bacilli. These anatomical facts, taken into consideration with the clinical observation that the blood pressure in diphtheria patients is often diminished, assume even greater significance when it is recalled that Marie's experiments and those of Stutzer suggest that the presence of diphtheria toxin in the circulation tends to exhaust the supply of epinephrin, the latter substance combining with the toxin to render it harmless.



nose and pharynx. In response, no doubt, to the same cause, the capillaries in the mucosa of the trachea, bronchi and bronchioles and, indeed, throughout the pulmonary parenchyma, are found at autopsy to be engorged, thus preparing the way, it would seem, for the entrance of any of the several varieties of bacteria which have been identified in the pneumonic lesions.

In the pathological laboratories of Bellevue Hospital I have had occasion to study two cases of so-called pandemic influenza in which death occurred without the intervention of pneumonic changes of other than negligible proportions. Both cases were observed near the close of the pandemic of last fall. In one case the signs of consolidation were limited to two or three small patches in the lower lobe of one lung, the largest approximating the size of one's thumb nail. In the other case there was a small focus in the middle lobe of the right lung. Consolidated areas of such limited extent could not possibly have occasioned the capillary injection which was found throughout the viscera. In view of the importance of such cases in establishing the fact that generalized visceral congestion precedes the pneumonic changes, I am presenting the clinical and anatomical data in some detail.

CASE I.—The patient, a man, aged forty-five years, was admitted to Bellevue Hospital with the statement that, five days previously, he had suffered a chill followed by violent headache, cough and mucopurulent expectoration, great prostration and generalized pains and aching sensations. At the time of admission to the hospital the patient's temperature was 103.8° F. and fluctuated between 101° and 104° F. throughout the six days that he was under observation. The blood pressure was 132 over 62. The respirations varied from 20 to 36, rising to 60 just before death, and the pulse rate was between 72 and 112. Physical examina-

tion showed an acutely ill man, breathing rapidly and laboriously, with prolonged wheezy expirations. The face, lips, and ears were cyanotic. The skin was the seat of a diffuse erythema and the mucosæ of the tonsils and pharynx were injected. Examination of the chest revealed diminution of the respiratory murmur throughout the pulmonary area. Expiration was prolonged, low pitched and wheezing, and sibilant and small moist râles were audible, particularly over the bases of the lungs. Physical signs of consolidation were not detected. On the eleventh day of his illness the patient, who was now markedly cyanotic, died with signs of pulmonary edema.

Autopsy (abbreviated protocol): On section, the skeletal muscles were raspberry red in color and dry. Both pleural cavities were free from fluid and adhesions and the pericardium was unchanged. The lungs were removed easily and the pleuræ were thin and glistening. The bronchi were bathed in mucopus and the mucosa was diffusely covered by a thin, whitish sheeting which, upon being removed, disclosed intense injection of the underlying capillaries with velvety swelling and edema of the membrane. The upper lobe of the left lung was injected and markedly edematous, but no areas of consolidation were found. The lower lobe of the left lung was rich in edematous fluid and embedded in its substance were two or three firm, deep bluish, consolidated patches, the largest approximating the size of a thumb nail. The right lung was essentially the same as the left, although no areas of consolidation were found. The peribronchial lymph nodes on both sides were edematous and congested. The spleen was somewhat enlarged, dull pink in color and its substance was almost diffuent in consist-

ence. Both suprarenal capsules were large, the medullæ intensely congested, dripping blood when incised. The kidneys were congested, the glomeruli standing out as minute reddish points and the cortical capillaries as delicate, reddish lines. The liver was likewise injected. Both sides of the heart were distended by huge quantities of bluish-black clotted and fluid blood.

CASE II.—The patient, a man aged twenty-four, was admitted to Bellevue Hospital in an irrational state. He was exceedingly restless. The face was cyanotic. It was learned of the patient that he had been ill for a period of about two weeks, during which time he had complained of aching sensations in the head and back. At the time of admission the patient's temperature was 103, the blood pressure was 112 over 70 and the white blood cells numbered 3,600. Respiration varied between 30 and 40 and the pulse rate between 84 and 120. Sibilant and small moist râles were audible over the pulmonary area, but no clinical indications of consolidation were found. The abdominal muscles and those of the extremities were rigid. Death occurred three days after admission with signs of pulmonary edema.

Autopsy (abbreviated protocol): On section the muscle tissues were well developed, raspberry red in color and dry. The belly of the rectus abdominis on both sides from pubes to umbilicus was infiltrated and disintegrated by bluish-black blood. The diaphragm was contracted into large, rigid folds. The heart was increased in size. The right side was immensely distended by bluish-black clotted and fluid blood and similar material, in smaller quantity, was released from the left side. The mucosa of the larger bronchi was covered by a grayish sheeting which, upon being removed, disclosed injection of the underlying capillaries and numbers of small hemorrhagic extravasations.



The upper lobes of the lungs were emphysematous, the lower lobes congested and edematous, releasing large amounts of grayish-red fluid on pressure. No sign of consolidation was detected in any portion of the lungs with the exception of a patch in the lower lobe of the right. This patch was about the size of a thumb nail and lay under the pleura, extending downward for a distance of about two cm. It was firm to the touch and airless, smooth, grayish-red in color, and exuded quantities of opaque, pinkish fluid on pressure. The spleen was slightly enlarged and congested throughout. Both suprarenals were enlarged, the medullæ swollen and velvety in appearance, bluish-black in color, dripping blood on being incised. The underlying coeliac ganglia were bright red in contrast to the pink of the normal. Both kidneys were universally congested, as were the liver and pancreas.

Microscopical examination was made of all the organs in both cases, but revealed nothing worthy of record in the present connection with the exception of the rectus muscle in the second case. This muscle was infiltrated by blood and its substance was disintegrated. The better preserved fibres were swollen, hyaline, and poorly nucleated, the changes corresponding to those seen in the same situation in the so-called Zenker's degeneration. Blood agar plates inoculated from the muscle at the time of autopsy were sterile after seventy-two hours. The natural inference seems to be that the rectus muscle had undergone degenerative changes of the sort more or less commonly encountered in such infections as typhoid fever, croupous pneumonia, influenza and the like and that the patient, who was exceedingly restless during his last illness, had sustained rupture of the altered fibres with subsequent hemorrhage.

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The commonest variety of pneumonia encountered in the recently prevailing pandemic infection was a rapidly progressive bilateral confluent lobular lesion, in which the brunt of injury was borne by the blood vessels. Hemorrhages were practically constant and occurred beneath the pleura and into the interstitial tissues of the lung, while the presence of free red cells in the alveoli constituted the most striking feature in the process of exudation. In a certain proportion of cases the exudate in the alveoli consisted almost entirely of red cells. At the same time the capillaries in the intervesicular tissues, as well as in the walls of the trachea, bronchi, and bronchioles, were injected to an extent rarely if, indeed, ever seen in any other variety of pneumonia. Further evidence of vascular injury was obvious in the form of inflammatory edema in which the escape of serum occurred not only in quantities in excess of those seen in any other variety of pneumonia, but the phenomenon was seldom missing.

In a second but smaller group of cases the lungs were the seat of a different type of pneumonia, namely, the acute productive bronchopneumonia of Delafield, which is likewise a bilateral process, at least in the majority of cases. It is characterized by the presence in the lungs of myriads of pinhead sized, grayish-white or cream colored foci which are rounded or angulated and in the centre of each of which a minute opening or depression is discernible.

On microscopical examination, it is found that each whitish spot corresponds to a small bronchus whose lumen is partially or completely filled by polynuclear leucocytes and desquamated epithelium. The connective tissue framework of the bronchiole supports numbers of dilated and injected capillary vessels, between which are more or less dense collections of round cells. The lumina of the bron-



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chioles and of the alveoli in the vicinity are filled, however, by polynuclear leucocytes or by leucocytes and desquamated cells. The later stages of this variety of pneumonia are attended, among other things, by the overgrowth of connective tissue in the smaller and medium sized bronchi, in the interalveolar septa and thus by permanent changes of a productive nature.

In still another series, mixed lesions occurred in the lungs. For example, it occasionally happened in our autopsy experience at Bellevue Hospital that a bilateral confluent lobular pneumonia of the lower lobes was associated with lesions of the bronchopneumonic form in, say, one upper lobe. In other instances the confluent lobular type of pneumonia was found in company with typical although limited lesions of the ordinary lobar variety.

The bacteriology of the recently prevailing pandemic disease varied no less than the pathology. In one group of cases the bacillus of influenza was isolated from the lungs, either in pure culture, or with other pathogenic microorganisms. In other cases streptococci, pneumococci, and the like were obtained in pure culture. The nearest approach to a common factor in the disease as a whole was to be found in the injection of the capillary system, not only in the lungs, but in other tissues. This, I believe, is the primary and fundamental effect of the causative agent. The opinion appears to be substantiated by the two cases here recorded in which death occurred without the intervention of pneumonic lesions of other than negligible proportions, and yet in both of which there was intense and widely disseminated capillary injection. As far as the pathogenesis of the several varieties of pneumonia is concerned, it would seem that injection of the capillary apparatus of the bronchial system together with exudative changes in the mucosa offer favorable condition for the entrance

of microorganisms into the pulmonary substance, the immediate reaction in the lung tissues depending, among other things, on the variety and virulence of the microorganism introduced. Moreover, the same process of reasoning seems applicable to the pathogenesis of certain other lesions associated with the so-called influenza, notably meningitis. In the autopsy rooms at Bellevue Hospital it was a common observation that the recently prevailing pandemic infection was attended by marked injection of the capillary vessels in the cerebral meninges. In three cases purulent meningitis was observed, always in company with a bilateral confluent lobular pneumonia. In one of these cases, a pure culture of a nonhemolytic streptococcus was obtained from the meningeal exudate; in a second there was a pure growth of the bacillus of influenza and in the third a pneumococcus. Thus it would appear that the vascular disturbances occasioned by injection of the smaller blood vessels in the meninges provide conditions which are no less propitious for the entrance of infective microorganisms than related changes in the vascular apparatus of the lungs.

The presence of hemorrhages, however, is by no means confined to the lungs. Epistaxis is frequent, sometimes profuse. In one case which was brought to my attention the patient was almost exsanguinated as a result of rupture of one of the smaller vessels in the nasal mucosa. In other instances blood may be present in the stools due, apparently, to the spontaneous rupture of overdistended capillaries in the intestinal mucous membrane. Varying grades of hematuria have been observed depending on the escape of blood either from the dilated capillaries in the substance of the kidney or from the congested mucous membrane of the pelvis, ureter, or bladder. In one of the Bellevue Hospital autopsies a large extravasation of blood was found in the mesentery, another in the soft tissues be-

hind the pericardium. In still another case the muscles of the right side of the chest near the costal slope were richly infiltrated by blood, and in several instances the lower belly of the rectus muscle was disintegrated by hemorrhage. In seven of the Bellevue cases slight jaundice of the conjunctivæ was observed. Inquiry showed that the mucous membrane of the duodenum was swollen and congested to an extent sufficient to impede the exit of bile through the papilla of Vater and thus, in part at least, to account for the jaundice.

CONCLUSIONS.

1. The cause of the so-called pandemic influenza has not yet been satisfactorily established.

2. The initial effect of the provocative agent appears to be exercised on the vascular system, bringing about an extraordinary degree of capillary dilatation and injection, not only in the skin and in certain of the visible mucous membranes, but throughout the viscera, simultaneously, or approximately so. At the same time the blood pressure is low and the pulse may be slow, even in patients who have not received digitalis. All of these facts combine to show that the circulatory action of the provocative agent is more complex than that of any known single poison. The occurrence of intense injection of the suprarenal medullæ is common, however, and is sometimes associated with hemorrhagic extravasations into the substance of the gland or even with thrombosis of the suprarenal veins. These changes in the suprarenal circulation offer at least a partial explanation for the low blood pressure and for the profound asthenia.

3. In certain respects the anatomical changes in the vascular system in the so-called influenza are comparable to those encountered in the same situations as a result of the action of poisons, notably in some cases of death from methyl alcohol and trinitrotoluene.



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4. The advent of pneumonic lesions in association with the so-called influenza is secondary to infection of the bronchi and bronchioles and of the intervesicular capillaries, these changes so lowering the resistance of the pulmonary tissues as to permit the entrance of infective microorganisms.

5. The presence of exudative lesions in the cerebral meninges in the so-called influenza is likewise to be explained on the basis of circulatory disturbances followed by the invasion of infective microorganisms.